Diastereoselective electrophilic \( \alpha \)-amination of camphor \( N^1 \)-acyl \( N^2 \)-phenylpyrazolidinones: the metal enolate-dependent synthesis of two possible hydrazide diastereomers

Chin-Sheng Chao, Chung-Kai Cheng, Ssu-Hsien Li, Kwunmin Chen

Department of Chemistry, National Taiwan Normal University, Taipei, Taiwan 116, Taiwan, ROC

**Abstract**

Complementary approaches under enolate amination reactions for the synthesis of both \( \alpha \)-hydrazidoacyl diastereomers have been achieved. Both isomers are obtained with high to excellent chemical yields and high stereoselectivities (up to >95:5 dr) when aryl-substituted camphor \( N^1 \)-acyl \( N^2 \)-phenylpyrazolidinone was treated with potassium hexamethyldisilylamide (KHMDS) and lithium hexamethyldisilylamide (LHMDS), respectively, followed by the addition of di-tert-butyl azodicarboxylate. The nondestructive removal of the chiral auxiliary, which can be carried out under mild condition, afforded the hydrazido alcohol with high enantiomeric ratio. The facial stereoselectivity and stereochemical course of the reactions are discussed.

The electrophilic \( \alpha \)-amination of carbonyl compounds constitutes one of the fundamental challenges in modern organic synthesis.\(^1\) Several asymmetric variants have been developed in recent years for the construction of the nitrogenous molecules by using azodicarboxylates as the nitrogen source. The resulting hydrazine derivatives serve as versatile precursors for the preparation of \( \alpha \)-amino acids, \( \alpha \)-hydrazino acids, and other important synthetic intermediates.\(^2\) The metal-based catalytic enantioselective \( \alpha \)-amination of \( N \)-acyloxazolidinones,\(^3\) \( \alpha \)-keto esters,\(^4\) and \( \beta \)-keto esters\(^5\) provides an easy entry to optically active \( \alpha \)-amino acids and \( \alpha \)-amino-\( \beta \)-hydroxy esters with high to excellent enantioselectivities. More recently, the organocatalytic electrophilic \( \alpha \)-amination of unmodified aldehydes, \( \alpha \)-cyanoacetate, and \( \beta \)-keto esters has also been reported.\(^6\) On the other hand, only limited examples of diastereoselective electrophilic amination of metal enolates have been documented.\(^7\) The metal enolate-based methodology for the carbon–nitrogen bond formation remained unexplored. Further, from a practical synthetic point of view, the preparation of both stereoisomers from the same chiral source has many synthetic advantages and has received considerable attention in recent years.\(^8\) The stereochemical outcomes can be influenced by several factors such as solvent, the structure of metal-substrate complex, and reagent components employed. We have recently developed a novel camphor-derived auxiliary, camphor \( N \)-phenyl pyrazolidinone, that has proved to be effective in asymmetric synthesis.\(^9\) We wish to report herein that electrophilic amination of chiral...
Aromatic hydrazide (1e) and its diastereomer (1f) were synthesized by reaction of the corresponding N,N-dimethylhydrazones with tert-butyl azodicarboxylate. In addition, the stereochemical feature of the α-amination is dependent on the presence of di-tert-butyl azodicarboxylate. The presence of this group allows the preparation of diastereomers with excellent chemical yield and high diastereoselectivity in the presence of a metal enolate. A careful analysis of the 1H NMR spectrum of the crude products for the determination of stereoselectivity. The spectrum of a purified hydrazide is interpretable, although with the presence of tautomers. A careful analysis of the 1H NMR spectrum of the crude products for the determination of stereoselectivity. This is due to the presence of the tautomeric forms caused by the restricted rotation about the Boc groups in the hydrazide, which has been documented in the literature. The spectrum of a purified hydrazide is interpretable, although with the presence of tautomers. A careful analysis of the 1H NMR spectrum of the crude products for the determination of stereoselectivity. The spectrum of a purified hydrazide is interpretable, although with the presence of tautomers. A careful analysis of the 1H NMR spectrum of the crude products for the determination of stereoselectivity. This is due to the presence of the tautomeric forms caused by the restricted rotation about the Boc groups in the hydrazide, which has been documented in the literature. The newly generated stereogenic center in the major diastereomer 2a was assigned as an S configuration by single crystallographic X-ray analysis.

In addition to the steric hindrance, the tautomeric equilibration of 2a in solution may also associate with the hydrogen bonds and the preferential disposition of the carbonyl dipoles. A close look of the X-ray crystallographic ORTEP structure of 2a shows that the NH forms hydrogen bonds with the nearby carbonyl groups.

To our surprise, the newly generated stereogenic center of the aminated adduct was reversed, when LHMDMS was used. Treatment of 1a with LHMDMS at −78 °C gave 3a as the major diastereomer with 90% de (entry 4). The distinct characteristics of 1H NMR spectrum in 3a are worth noting. In addition to the two signals of the hydrazide NH proton at 6.68 and 6.49 ppm, the C-5 methine proton also appeared as a set of two signals at 4.41 and 4.31 ppm, respectively, in the same ratio of 1.8:1.0, similar to that of NH signals. The significant chemical shift difference of C-5 proton signal in 1H NMR spectrum between hydrazides 2a (3.49 ppm) and 3a (4.41 and 4.31 ppm) can be attributed to the diaframatic anisotropy effect of the phenyl substituent. This represents, to the best of our knowledge, the first example of a complementary electrophilic α-amination reaction for the synthesis of both diastereomeric hydrazides by simply changing the base. Having developed reaction conditions that afford complementary diastereomers in the amination reactions, we sought to test the scope and feasibility of the auxiliary architecture.

![Diagram of the reaction](image-url)

**Scheme 1.** Recovery of chiral auxiliary from hydrazides 2a and 3a.
This complementary amination process is applicable to various aryl-substituted substrates 1b–e. Toward this end, good to high levels of stereoselectivities of the aminating adducts with S configuration (except for 2e due to the priority numbering) were obtained, when 1b–e were treated with KHMDS followed by the addition of di-tert-butyl azodicarboxylate (entries 7, 9, 11, and 13). The $^1$H NMR signal of the corresponding C-5 methine proton in 2b–e consistently appeared in a range of 3.50–3.62 ppm. On the other hand, reversal of stereoselectivity of the aminated adducts 3b–e (R configuration, except for 3e) was observed when LHMDS was used under the same conditions (entries 8, 10, 12, and 14). The $^1$H NMR signal of the C-5 methine protons in 3b–e appears in a range of 4.41–4.53 ppm as expected. The characteristic features of the $^1$H NMR spectra of the hydrazides 2 and 3 permitted the assignment of the newly generated stereogenic centers. No reaction occurred when a bulky substituent 1f (R = tert-butyl) was used. To complete one cycle of the chiral auxiliary, the aminated adducts (S)-2a and (R)-3a were then subjected to reduction conditions. Exposure of 2a to NaBH$_4$ in THF at ambient temperature provided the desired hydrazido alcohol (S)-4 (65%) ([$\delta$]$_{3}$-34.5 (c 1.0, CHCl$_3$)) and camphor N$_2$-phenylpyrazolidinone was recovered in 84% yield (Scheme 1). Similar conditions were applied to give (R)-4 ([$\delta$]$_{3}$-39.0 (c 1.0, CHCl$_3$)) with 82% yield, when 3a was used.

The mechanistic explanation for the asymmetric amination has not yet been elucidated at this moment and can be rationalized by the structurally well-defined metal enolate geometries in the transition states as depicted in Figure 3.$^{24}$ The hydrogen bond formed between the $\alpha$-hydrogen and the carbonyl group of di-tert-butyl azodicarboxylate may play a role in stabilizing the favored enolate complexes. The eight-membered potassium Z-enolate is preferentially formed, when 1a is treated with KHMDS to give the corresponding adduct 2a. On the other hand, the six-membered lithium E-enolate is energetically favored, when LHMDS is used, resulting in the formation of 3a as the major isomer. The size of the metal counterion may also be important in forming the eight-membered and six-membered enolates.

An interesting imino intermediate 5 was isolated, when the amination reaction was carried out at −78 °C followed by warm up to 0 °C gradually (Scheme 2). When phenylacetyl-substituted pyrazolidinone 1a was treated with KHMDS and di-tert-butyl azodicarboxylate at −78 °C and warmed up to 0 °C over a period of 5 h, the imino product 5 was isolated with high chemical yield. On the other hand, when the reaction temperature was raised to −30 °C, hydrazide 2a was isolated as the major product (70%), and the imino intermediate 5 was obtained with 20% chemical yield. Tributyltin hydride reduction of 5 in THF afforded the Boc-protected (R)-$\alpha$-amino product 6 (70% de) as the major diastereomer in a total of 83% chemical yield. The hydride attacks from the bottom face of the imino functionality in 5.$^{12}$

In conclusion, complementary metal enolate amination of the auxiliary-derived N-acyls was developed for the synthesis of two possible hydrazide diastereomers. Either isomer can be obtained with excellent chemical yield and high diastereoselectivity (up to 90% de), when aryl-substituted camphor N$_2$-acyl N$_2$-phenylpyrazolidinones are treated with KHMDS and LHMDS, respectively, followed by the addition of di-tert-butyl azodicarboxylate. This extends the synthetic applications to the versatile and general utility of camphor N$_2$-phenylpyrazolidinone as a good stereocontrolling element in diastereoselective reaction.

**Acknowledgments**

This work was supported by the National Science Council of the Republic of China (NSC 96-2113-M-003-005-MY3) and the National Taiwan Normal University (96TOP001). Our gratitude goes to the Academic Paper Editing Clinic, NTNU, and we are also grateful to the National Center for High-Performance Computing for computer time and facilities.

**Supplementary data**

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.11.003.

**References and notes**


10. Variable-temperature 1H NMR studies of 2a showed that the conformeric ratio increases with increasing temperature. For example, the conformeric ratio of hydrazide 2a is 1.5 when the spectrum was recorded at −15 °C. The ratio was increased to 1.7 (at 5 °C), to 1.9 (at 25 °C) and further to 2.3 (at 55 °C). Interestingly, a third conformer appears when the temperature was decreased to −55 °C.


12. The absolute stereochemistry of the minor (5)-α-amino diastereomer 6 was confirmed by single crystallographic X-ray analysis.